

Treatment of herpes zoster

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ABSTRACT

OBJECTIVE To review the evidence regarding treatment of herpes zoster (HZ) in the short-term, focusing on the prevention of postherpetic neuralgia (PHN).

QUALITY OF EVIDENCE The evidence relating to treatment of HZ is derived mainly from randomized controlled trials (level I evidence).

MAIN MESSAGE Antiviral drugs might have some effect on the severity of acute pain and on the duration of skin lesions. Corticosteroids also alleviate acute pain. Oral antiviral medication reduces the risk of eye complications in patients with ophthalmic HZ. There is no convincing evidence that antiviral medication reduces the risk of PHN. Some studies, however, have shown that famciclovir and valacyclovir shorten the duration of PHN. The effectiveness of amitriptyline or cutaneous and percutaneous interventions in preventing PHN has not been proven.

CONCLUSION Oral antiviral drugs should be prescribed to elderly HZ patients with high risk of PHN. Moreover, these drugs should be prescribed to all patients at the first signs of ophthalmic HZ, irrespective of age or severity of symptoms.

RÉSUMÉ

OBJECTIF Revoir les données sur le traitement à court terme de l'herpes zoster (HZ), en insistant particulièrement sur la prévention de la névralgie post-herpétique (NPH).

QUALITÉ DES PREUVES Les données probantes sur le traitement de l'HZ proviennent principalement d'essais randomisés contrôlés (preuves de niveau I).

PRINCIPAL MESSAGE Les antiviraux pourraient avoir un certain effet sur l'intensité de la douleur aiguë et sur la durée des lésions cutanées. Les corticostéroïdes soulagent aussi la douleur aiguë. Les antiviraux oraux diminuent le risque de complication oculaires chez les patients souffrant de zona ophtalmique. Il n'y a pas de données convaincantes qui laissent croire que la médication antivirale puisse réduire le risque de NPH. Certaines études ont toutefois montré que le famciclovir et le valacyclovir réduisent la durée de la NPH. L'efficacité de l'amitriptyline ou des interventions cutanées ou percutanées pour prévenir la NPH n'a pas été prouvée.

CONCLUSION Il y a lieu de prescrire des antiviraux chez les patients âgés souffrant d'HZ qui présentent un risque élevé de NPH. Cette médication devrait en outre être prescrite à tout patient dès les premiers signes de zona ophtalmique, quels que soient l'âge ou l'intensité des symptômes.

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Herpes zoster (HZ), also known as shingles, is the secondary manifestation of an earlier infection with the varicella-zoster virus in one or more dermatomes. The reported incidence varies from 2.2 to 3.4 per 1000 people per year.¹⁻³ As reactivation of the virus is linked to an age-related diminished virus-specific and cell-mediated immunity, HZ develops mainly in elderly people. Immunocompromised patients are also at increased risk of developing HZ. As it has not yet been proven that HZ is provoked by any serious underlying pathologic condition (eg, malignancy),⁴ a search for possible risk factors is not warranted in otherwise healthy patients in whom HZ develops.

The main complications of HZ include postherpetic neuralgia (PHN) and ophthalmic problems, the latter in cases of ophthalmic HZ. Postherpetic neuralgia is usually defined as pain in the involved dermatome that is still present 1 month after rash onset.^{5,6} Sometimes, however, a period of 3 months is applied.^{7,8} A large prospective study identified 4 independent predictors of PHN: older age, severe acute pain, severe rash, and a shorter duration of rash before consultation.⁹ Although PHN can disappear after a few months, it can also develop into a lasting persistent pain syndrome.

A recent double-blind placebo-controlled trial showed that vaccination of immunocompetent persons 60 years of age and older with an investigational live attenuated zoster vaccine markedly decreased HZ morbidity and PHN incidence.⁸

The aim of this article is to review the evidence regarding treatment of immunocompetent HZ patients, focusing on short-term as well as on long-term (prevention of PHN) effects.

Quality of evidence

In October 2006, we searched the Cochrane Controlled Trial Register (key word *herpes zoster*) and MEDLINE (MeSH terms *herpes zoster* and *therapy*) for randomized controlled trials (RCTs), meta-analyses, and reviews. We selected only those articles written in English and disregarded any studies of immunocompromised patients. Moreover, the assessed treatment had to be feasible in outpatient health care. Without language restriction we found 281 MEDLINE hits, of which 20 were not written in English. These concerned mainly reviews and, based on titles and abstracts, none of them added information to what was available in the English publications.

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Effects of treatment in the short-term

Antiviral medication. Most of the placebo-controlled RCTs of antiviral therapy were summarized in a meta-analysis.¹⁰ A subanalysis (4 studies¹¹⁻¹⁴ comprising 692 patients) showed that acyclovir (800 mg 5 times daily for 7-10 days) had no statistically significant effect on acute pain after 1 month (pooled odds ratio 0.83, 95% confidence interval [CI] 0.58 to 1.21). Because the various studies used measurement methods that could not be compared, no overall effect on the duration of acute pain could be established. From the separate studies, however, it appeared that the effect of acyclovir on the duration of acute pain did reach statistical significance in a few instances. Pain relief was seen at most a few days earlier. Another placebo-controlled RCT with acyclovir, published after this meta-analysis, also did not demonstrate a statistically significant effect on pain reduction after 1 month.¹⁵

A double-blind placebo-controlled RCT with famciclovir (500 or 750 mg 3 times a day for 1 week) reported that the median length of time to the disappearance of acute pain did not differ significantly among the 3 groups.¹⁶ It only reported a statistically significant effect on pain in the subgroup of patients with more than 50 skin lesions given famciclovir in the lowest dose. The median length of time for pain to disappear was 20 days in this subgroup compared with 30 days in the placebo group (hazard ratio 1.9, 95% CI 1.3 to 3.0). Data from a double-blind acyclovir-controlled RCT showed that famciclovir administered once (750 mg) or twice (500 mg) daily was as effective as famciclovir (250 mg) 3 times daily, and as effective as acyclovir (800 mg) 5 times daily, in cutaneous healing and reduction of acute pain.¹⁷ A small double-blind acyclovir-controlled RCT showed that famciclovir (250 mg 3 times a day) was as effective as acyclovir (800 mg 5 times a day) for healing skin lesions and decreasing acute pain.¹⁸ Another study compared valacyclovir with acyclovir.¹⁹ The design of that study does not allow for conclusions on the reduction of acute pain.

In most individual studies the time necessary for the vesicles, ulcers, and crusts to disappear was shorter when antiviral medication was used than when placebo was used. The time gain was only 1 or 2 days. Antiviral medication might relieve acute pain and speed healing of skin lesions. These effects are only marginal, though, and thus have little clinical relevance.

Levels of evidence

Level I: At least one properly conducted randomized controlled trial, systematic review, or meta-analysis

Level II: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study

Level III: Expert opinion or consensus statements

All trials reported the same frequencies of side effects (eg, headache in 11% to 23% of patients and nausea in 12% to 16% of patients^{15,16,19}) for both antiviral medication and placebo.

Corticosteroids. There is no thorough meta-analysis of studies on the effects of corticosteroids. One large RCT compared the effects of acyclovir with those of the combination acyclovir and prednisolone.²⁰ The addition of prednisolone (40 mg/d for 3 weeks, tapering) to acyclovir resulted in a statistically significant reduction of pain during the first 2 weeks (average pain score, on a scale of 0 to 5, had diminished by 1.4 in the prednisolone group and by 1.0 in the non-prednisolone group on day 7; the reductions were 1.8 and 1.5, respectively, on day 14). No further statistically significant differences were found after 2 weeks. Moreover, a significantly higher percentage of the skin lesions had been cured in the prednisolone group ($P=.02$) on day 7 and day 14, although the duration of complete recovery did not differ significantly between the 2 groups. Another RCT compared acyclovir-prednisone, acyclovir-placebo, prednisone-placebo, and placebo-placebo combinations.¹⁵ Patients who received prednisone (60 mg/d for 3 weeks, tapering), whether or not in combination with acyclovir, had a 2.3 times (95% CI 1.4 to 3.5) greater chance of being free of pain after 1 month than patients who did not receive prednisone. Quicker healing of skin lesions was not observed. Corticosteroids, therefore, only somewhat relieve acute pain.

All studies reported side effects of corticosteroids. The most common were dyspepsia (5% in the prednisolone group, <1% in the acyclovir group), nausea (2% and 1%, respectively), headache (1% and 0%, respectively), and edema (3% and 0%, respectively).²⁰ The theoretically feared dissemination of the localized HZ was not observed.

Other therapeutic options. An open RCT assessed the effectiveness of a single epidural injection of corticosteroids (80 mg methylprednisolone) and local anesthetics (10 mg bupivacaine) in the acute phase of HZ for HZ-associated pain.²¹ One month after randomization, 48% of the patients in the intervention group reported HZ-associated pain versus 58% in the control group (relative risk 0.83, 95% CI 0.71 to 0.97). Moreover, intervention reduced the intensity of pain (median score on a 100-point visual analog scale 2 [25th–75th percentile 0 to 23] in the intervention group vs 6 [0 to 32] in the control group [$P=.02$]). The effect of the epidural injection, however, did not last beyond 1 month. Therefore, epidural injection should only be considered for patients with severe acute pain from HZ who are not responding to standard analgesic therapy.

No patient had serious adverse events related to the epidural injection.

Effects of treatment on prevention of postherpetic neuralgia

Antiviral medication. There is no convincing evidence that acyclovir influences the incidence or duration of PHN. Three placebo-controlled RCTs on acyclovir (800 mg 5 times daily for 7 days¹³ and 10 days^{11,14}) reported less pain in the treatment groups in the short-term (1–3 months), but no difference in the long-term (more than 3 months). Another study compared valacyclovir with acyclovir.¹⁹ Three groups were used: valacyclovir 1000 mg 3 times a day for 7 days, valacyclovir 1000 mg 3 times a day for 14 days, and acyclovir 800 mg 5 times daily for 7 days. The median length of time for pain to disappear was 38 and 44 days in the groups treated with valacyclovir for 7 or 14 days, respectively, and 51 days in the group treated with acyclovir. There was no statistically significant difference among the various groups with respect to PHN occurrence, although the postherpetic pain lasted longer among those in the acyclovir group than among those in the group treated with valacyclovir for 7 days (hazard ratio 1.3, 95% CI 1.0 to 1.6). Famciclovir also had no effect on PHN incidence. However, a well-designed placebo-controlled RCT did show that the duration of pain in those patients who developed PHN was notably shorter (63 days in the famciclovir group vs 119 days in the placebo group; 63 vs 163 days among patients >50 years).¹⁶ After 6 months, pain was reported by 15% of the patients in the group treated with famciclovir compared with 23% of those in the placebo group. According to these data, 12 patients must be treated with famciclovir in order to gain 1 additional patient free of pain after 6 months.

Other therapeutic options. Corticosteroids have not been shown to influence the occurrence or duration of PHN.^{15,20,22} A small placebo-controlled RCT showed that treatment with amitriptyline (25 mg before bedtime for 90 days) during the acute stage of HZ reduced the risk of PHN by half.²³ Further evidence, however, is lacking. The efficacy of cutaneous (eg, topical local anesthetics) and percutaneous (eg, sympathetic and epidural blocks) interventions on the prevention of PHN has not been established.^{21,24}

Effects of treatment of ophthalmic herpes zoster

Oral antiviral medication. Ophthalmic HZ is a potentially serious disease that can result in severe and lasting pain, particularly among elderly patients. Moreover, without antiviral treatment, about half of all patients will develop various eye disorders. Conjunctivitis, for example, is seen in nearly all HZ patients with ocular involvement. More severe disorders include keratitis, uveitis, and optic neuritis of the affected eye. If these latter disorders are not diagnosed and treated adequately, the patient's sight might be permanently affected. Early

(within 72 hours after rash onset) treatment with acyclovir (800 mg 5 times a day for 7 days) reduces the percentage of eye disorders in ophthalmic HZ patients from 50% to between 20% and 30% (eg, 25% of the patients in the acyclovir group developed stromal keratitis vs 56% in the control group; $P=.008$).²⁵ Valacyclovir (1000 mg 3 times daily) and famciclovir (500 mg 3 times daily) seem to be as effective as acyclovir in reducing HZ-associated pain,^{26,27} but their efficacy in reducing eye disorders associated with HZ has not been studied. In clinical practice, however, these second-generation antiviral agents might be more effective than acyclovir because patients are more likely to comply with the treatment regimen (3 rather than 5 daily doses). The efficacy of antiviral medication initiated more than 72 hours after the onset of skin rash has never been confirmed. Nevertheless, prescription of these drugs after this time span should be considered among elderly patients with ophthalmic HZ, because their immune responses are usually delayed and, consequently, viral shedding can last longer (level III evidence).²⁸ As the course of disease is unpredictable, prescription of oral antiviral drugs at the first signs of infection is recommended for all patients with ophthalmic HZ, irrespective of their age or the severity of symptoms.²⁹

Antiviral eye ointment. Although the additional effectiveness of acyclovir eye ointment has never been established, topical acyclovir can be considered in cases of severe eye infection, as much higher concentrations of the drug in the anterior eye segment will be achieved by this route. Monotherapy with antiviral ointment is, however, insufficient and should be adjuvant to oral treatment.³⁰

Other therapeutic interventions. Anesthesia-based interventions, such as stellate ganglion block,³¹ might produce short-term pain relief but are not done on a regular basis. In addition, no evidence exists for their effectiveness in reducing the risk of protracted pain.

Conclusion

In most cases, HZ is self-limiting and treatment with analgesics suffices. Based on level I evidence, antiviral medication might have some effect on the severity of acute pain and the duration of skin lesions. Corticosteroids also alleviate some of the acute pain. Oral antiviral medication reduces the risk of eye complications in patients with ophthalmic HZ. The most frequent complication of HZ, especially in the elderly, is PHN. There is no convincing evidence that antiviral medication reduces the risk of this complication. Some studies, however, have shown that famciclovir and valacyclovir shorten the duration of PHN. It has not yet been proven that corticosteroids, amitriptyline, and cutaneous and percutaneous interventions are effective in preventing PHN.

EDITOR'S KEY POINTS

- Herpes zoster (HZ) is the secondary manifestation of an earlier infection with the varicella-zoster virus that occurs mainly among elderly and immunocompromised patients.
- The most common complications of HZ include postherpetic neuralgia and ophthalmic problems.
- In most cases, HZ is self-limiting and treatment with analgesics is adequate. Antiviral medication and corticosteroids might have some effect on the severity of acute pain and, in the case of antiviral agents, might reduce the duration of skin lesions.
- There is no convincing evidence that antiviral medication, corticosteroids, amitriptyline, or cutaneous and percutaneous interventions reduce the risk of postherpetic neuralgia.
- Oral antiviral medication reduces the risk of eye complications in patients with ophthalmic HZ and might shorten the duration of postherpetic neuralgia.

POINTS DE REPÈRE DU RÉDACTEUR

- L'herpes zoster (HZ) est la manifestation secondaire d'une infection antérieure au virus de la varicelle qui survient surtout chez les patients plus âgés ou immunodéprimés.
- Les complications les plus fréquentes de l'HZ incluent la névralgie post-herpétique et les problèmes ophtalmiques.
- Dans la plupart des cas, l'HZ guérit spontanément et se traite adéquatement par des analgésiques. La médication antivirale et les corticostéroïdes pourraient avoir un effet sur l'intensité de la douleur aiguë; les antiviraux, pour leur part, pourraient réduire la durée des lésions cutanées.
- Il n'y a pas de preuves convaincantes que la médication antivirale, les corticostéroïdes, l'amitriptyline ou les interventions cutanées ou précutanées diminuent le risque de NPH.
- La médication antivirale orale réduit le risque de complication oculaire dans l'HZ ophtalmique et pourrait réduire la durée de la NPH.

Competing interests

None declared

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